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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	SEP 09	CA/CAplus records now contain indexing from 1907 to the present
NEWS 4	DEC 08	INPADOC: Legal Status data reloaded
NEWS 5	SEP 29	DISSABS now available on STN
NEWS 6	OCT 10	PCTFULL: Two new display fields added
NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
NEWS 15	DEC 18	BIOTECHNO no longer updated
NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 22	FEB 05	German (DE) application and patent publication number format changes
NEWS 23	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 24	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 25	MAR 03	FRANCEPAT now available on STN

NEWS EXPRESS	MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
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FILE 'HOME' ENTERED AT 09:34:41 ON 29 MAR 2004

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:34:47 ON 29 MAR 2004
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STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7
DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> s rrrrrwgrrrrrr/sqsp
L1 4 RRRRRWGRRRRRR/SQSP

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	26.92	27.13

FILE 'HCAPLUS' ENTERED AT 09:35:23 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 28 Mar 2004 (20040328/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s l1
L2             1 L1

=> d l1 ibib abs
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y


'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats.  The predefined substance formats
are:  (RN = CAS Registry Number)

REG     - RN
SAM     - Index Name, MF, and structure - no RN
FIDE    - All substance data, except sequence data
IDE     - FIDE, but only 50 names
SQIDE   - IDE, plus sequence data
SQIDE3  - Same as SQIDE, but 3-letter amino acid codes are used
SQD     - Protein sequence data, includes RN
SQD3    - Same as SQD, but 3-letter amino acid codes are used
SQN     - Protein sequence name information, includes RN

CALC    - Table of calculated properties
EPROP   - Table of experimental properties
PROP    - EPROP and CALC

Any CA File format may be combined with any substance format to
obtain CA references citing the substance.  The substance formats
must be cited first.  The CA File predefined formats are:

ABS  -- Abstract
APPS -- Application and Priority Information
BIB  -- CA Accession Number, plus Bibliographic Data
CAN  -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND  -- Index Data
IPC  -- International Patent Classification
PATS -- PI, SO
STD  -- BIB, IPC, and NCL

IABS --ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when
it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented,
with text labels.
```

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

=> d his

(FILE 'HOME' ENTERED AT 09:34:41 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 09:34:47 ON 29 MAR 2004
L1 4 S RRRRRWGRRRRRR/SQSP

FILE 'HCAPLUS' ENTERED AT 09:35:23 ON 29 MAR 2004
L2 1 S L1

FILE 'REGISTRY' ENTERED AT 09:35:44 ON 29 MAR 2004

FILE 'HCAPLUS' ENTERED AT 09:36:33 ON 29 MAR 2004

=> d l2 ibib abs

L2 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:116428 HCAPLUS
DOCUMENT NUMBER: 136:330460
TITLE: Protamine-Fragment Peptides Fused to an SV40 Nuclear Localization Signal Deliver Oligonucleotides That Produce Antisense Effects in Prostate and Bladder Carcinoma Cells
AUTHOR(S): Benimetskaya, Luba; Guzzo-Pernell, Nancy; Liu, Su-Ting; Lai, Johnathan C. H.; Miller, Paul; Stein, C. A.
CORPORATE SOURCE: Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, 3052, Australia
SOURCE: Bioconjugate Chemistry (2002), 13(2), 177-187
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The development of antisense technol. has focused on improving methods for oligonucleotide delivery into cells. In the present work, we describe a novel strategy for oligonucleotide delivery based on a bifunctional peptide composed of a C-terminal protamine-fragment that contains a DNA-binding domain and an N-terminal nuclear localization signal sequence derived from the SV40 large-T antigen (The sequences of two of the peptides are R6WGR6-PKKKRKV [s-protamine-NLS] and R4SR6FGR6VWR4-PKKKRKV [l-protamine-NLS]). We demonstrated, by intrinsic fluorescence quenching, that peptides of this class form complexes with oligodeoxynucleotides. To evaluate delivery, we used a 20-mer phosphorothioate oligomer (Isis 3521) targeted to the 3'-untranslated region of the PKC-α mRNA and G3139, an 18-mer phosphorothioate targeted to the first six codons of the human bcl-2 open reading frame, and complexed them with either of two peptides (s- or l-protamine-NLS). These peptides bind to and deliver antisense oligonucleotides to the nucleus of T24 bladder and PC3 prostate cancer cells, as demonstrated by confocal microscopy. Furthermore, as shown by Western and Northern blotting, the peptide-oligonucleotide complexes produced excellent downregulation of the expression of the complementary mRNAs, which in turn resulted in downregulation of protein expression. However, under certain circumstances (predominately in PC3 cells), incubation of the cells with chloroquine was required to produce antisense

activity. Using this strategy, PKC-α protein and mRNA expression in T24 and PC3 cells and bcl-2 expression in PC3 cells was reduced by approx. 75±10% at a min. concentration of oligomer of 0.25 μM, in combination with 12-15 μM peptide. On the basis of our results, we conclude that arginine-rich peptides of this class may be potentially useful delivery vehicles for the cellular delivery of antisense oligonucleotides. This new strategy may have several advantages over other methods of oligonucleotide delivery and may complement already existing lipid-based technologies.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL MEDLINE BIOSIS EMBASE CA SCISEARCH

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.26	37.17

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CA SUBSCRIBER PRICE	-0.69	-0.69

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=> s ((1 or l) (n) protamine?)
L3 985 ((1 OR L) (N) PROTAMINE?)

=> s ((s) (n) protamine?)
MISSING TERM '((S'
The search profile entered contains a left parenthesis,
'(' followed by an operator.

=> s (s (n) protamine?)
L4 80 (S (N) PROTAMINE?)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 28 DUP REM L4 (52 DUPLICATES REMOVED)

=> s l5 and py<=2002
2 FILES SEARCHED...
L6 27 L5 AND PY<=2002

=> d l6 ibib abs

L6 ANSWER 1 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2002200709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11906253
TITLE: Protamine-fragment peptides fused to an SV40 nuclear

localization signal deliver oligonucleotides that produce antisense effects in prostate and bladder carcinoma cells.

AUTHOR: Benimetskaya Luba; Guzzo-Pernell Nancy; Liu Su-Ting; Lai Johnathan C H; Miller Paul; Stein C A

CORPORATE SOURCE: Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria, 3052, Australia.

CONTRACT NUMBER: R01 GM58791 (NIGMS)

SOURCE: Bioconjugate chemistry, **(2002 Mar-Apr)** 13 (2) 177-87.
Journal code: 9010319. ISSN: 1043-1802.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200207

ENTRY DATE: Entered STN: 20020406
Last Updated on STN: 20020724
Entered Medline: 20020723

AB The development of antisense technology has focused on improving methods for oligonucleotide delivery into cells. In the present work, we describe a novel strategy for oligonucleotide delivery based on a bifunctional peptide composed of a C-terminal protamine-fragment that contains a DNA-binding domain and an N-terminal nuclear localization signal sequence derived from the SV40 large-T antigen (The sequences of two of the peptides are R6WGR6-PKKKRKV [**s-protamine**-NLS] and R4SR6FGR6VWR4-PKKKRKV [l-protamine-NLS]). We demonstrated, by intrinsic fluorescence quenching, that peptides of this class form complexes with oligodeoxynucleotides. To evaluate delivery, we used a 20-mer phosphorothioate oligomer (Isis 3521) targeted to the 3'-untranslated region of the PKC-alpha mRNA and G3139, an 18-mer phosphorothioate targeted to the first six codons of the human bcl-2 open reading frame, and complexed them with either of two peptides (s- or l-protamine-NLS). These peptides bind to and deliver antisense oligonucleotides to the nucleus of T24 bladder and PC3 prostate cancer cells, as demonstrated by confocal microscopy. Furthermore, as shown by Western and Northern blotting, the peptide-oligonucleotide complexes produced excellent downregulation of the expression of the complementary mRNAs, which in turn resulted in downregulation of protein expression. However, under certain circumstances (predominantly in PC3 cells), incubation of the cells with chloroquine was required to produce antisense activity. Using this strategy, PKC-alpha protein and mRNA expression in T24 and PC3 cells and bcl-2 expression in PC3 cells was reduced by approximately 75 +/- 10% at a minimum concentration of oligomer of 0.25 microM, in combination with 12-15 microM peptide. On the basis of our results, we conclude that arginine-rich peptides of this class may be potentially useful delivery vehicles for the cellular delivery of antisense oligonucleotides. This new strategy may have several advantages over other methods of oligonucleotide delivery and may complement already existing lipid-based technologies.

=> d 16 ibib abs 2-26

L6 ANSWER 2 OF 27 MEDLINE on STN

ACCESSION NUMBER: 2001372362 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11429331

TITLE: The effects of heparin, protamine, and heparin/protamine reversal on platelet function under conditions of arterial shear stress.

AUTHOR: Griffin M J; Rinder H M; Smith B R; Tracey J B; Kriz N S; Li C K; Rinder C S

CORPORATE SOURCE: Departments of Anesthesiology, Laboratory Medicine,

Internal Medicine, and Pediatrics, Yale University School of Medicine and Yale-New Haven Hospital, New Haven, Connecticut 06520-8051, USA.. michael.griffin@yale.edu
SOURCE: Anesthesia and analgesia, **(2001 Jul)** 93 (1) 20-7.
Journal code: 1310650. ISSN: 0003-2999.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Platelet dysfunction contributes to blood loss after cardiopulmonary bypass. This study examined the antiplatelet effects of heparin, protamine, and varying heparin/protamine ratios in an in vitro physiologic model and further elucidated the mechanism of the antiplatelet and anticoagulant effects of protamine. We used the Clot Signature Analyzer (CSA(TM)), a system that analyzes coagulation in flowing whole blood, to test two aspects of platelet function, with different concentrations of heparin and protamine, under conditions simulating arterial flow: collagen-induced thrombus formation (CITF) under moderate shear and high shear platelet activation, platelet hemostasis time (PHT). In addition, platelet aggregometry, celite activated clotting time (Hepcon(TM) ACT), prothrombin time (PT), and partial thromboplastin time (PTT) were measured. Both PHT and the CITF were prolonged by heparin at 20 microg/mL, protamine at 20 and 40 microg/mL, and heparin/protamine ratios of 1:1 and 1:2, but not at 1:1.5. The Hepcon ACT was prolonged by heparin 20 microg/mL and protamine alone at 20 and 40 microg/mL, was normal at a ratio of 1:1, and was prolonged at 1:1.5 and 1:2. Protamine 80 microg/mL prolonged the PT and PTT. Dependency on thrombin, protein kinase C activation, and nonspecific charge effects were examined. The direct thrombin inhibitor D-phenylalanyl-L-prolyl-L-arginyl-chloromethyl ketone prolonged the PHT and ACT, but not the CITF, whereas the polycationic molecules polyarginine and polylysine prolonged the CITF, but not the PHT. The effect of protamine on the PTT, but not PT, could be shortened by the addition of excess phospholipid. Therefore, heparin inhibits both high shear collagen-independent and moderate shear collagen-dependent platelet activation; however, the latter is not mediated by its antithrombin activity. **Protamine's** antithrombin effect may explain its inhibition of platelet activation at high shear stress. **Protamine's** nonspecific charge effects are more important for inhibiting moderate shear collagen-induced platelet activation. Implications: This study suggests that protamine reversal of heparin's antiplatelet effect occurs within a narrow window because of the direct antiplatelet effects of protamine. Antithrombin effects may explain the inhibition of shear activation of platelets by both heparin and protamine. Nonspecific charge effects of protamine may explain the inhibition of collagen platelet activation in the presence of medium shear.

L6 ANSWER 3 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2000076837 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10607857
TITLE: Development of heparin antagonists with focused biological activity.
AUTHOR: Shenoy S; Harris R B; Sobel M
CORPORATE SOURCE: Commonwealth Biotechnologies, Inc., 601 Biotech Dr., Richmond, VA 23235, USA.
SOURCE: Current pharmaceutical design, **(1999 Dec)** 5 (12) 965-86. Ref: 56
Journal code: 9602487. ISSN: 1381-6128.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000211

AB Heparin, a complex glycosaminoglycan, has long been used to temporarily render the blood incoagulable during extracorporeal circulation, cardiovascular surgery, and other arterial interventions. But bleeding complications are especially common when the arterial tree is violated, occurring in as many as 10-15% of cases. For cardiovascular surgery and many related interventions, protamine has long been the standard antagonist when acute and complete neutralization of heparin s anticoagulant effect is necessary. **Protamine s** efficacy is related in part to its total net cationic charge, but unfortunately so is its toxicity. For these reasons, there is renewed interest in developing heparin antagonists which will replace the use of protamine. At Commonwealth Biotechnologies, Inc., we have used a rationale design approach for the preparation of a family of low molecular weight helix peptides which bind heparin with high affinity. For each of the new compounds, we have assessed their ability to bind heparin using isothermal titration calorimetry and circular dichroism spectrometry and have examined potential complexes formed with the anticoagulant pentasaccharide unit of heparin using molecular modeling techniques. The biological potencies of these compounds were assessed in ex vivo experiments where their ability to compete with antithrombin for binding heparin was determined. The best of the compounds, designated HepArrestTM, is highly effective in reversing heparin-mediated and HepArrest is a safer drug than protamine because of reduced adverse hemodynamic side effects compared with those associated with protamine. HepArrest binds low molecular weight heparins and causes reversal of anticoagulation by low molecular weight heparins, as determined by activated partial thromboplastin time, thrombin time, or factor Xa neutralization assays. These highly promising preclinical results indicate that HepArrest is a novel heparin neutralizing agent that may well fill a substantial unmet need for vascular surgeons and cardiac anesthesiologists who perform coronary artery bypass grafts and several other major vascular surgeries, as well as for cardiologists and interventional radiologists.

L6 ANSWER 4 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1999422062 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10490770
TITLE: Use of protamine to augment adenovirus-mediated cancer gene therapy.
AUTHOR: Lanuti M; Kouri C E; Force S; Chang M; Amin K; Xu K; Blair I; Kaiser L; Albelda S
CORPORATE SOURCE: Department of Surgery, Thoracic Oncology Research Laboratory, Philadelphia, PA, USA.
CONTRACT NUMBER: PO166726
SOURCE: Gene therapy, **(1999 Sep)** 6 (9) 1600-10.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413

Entered Medline: 20000403

AB Improving the therapeutic potential of adenoviral (Ad) suicide gene therapy has become an area of intense investigation since the inception of gene therapy strategies for cancer treatment. Poor efficiency of gene transfer to target tissues has become one of the most important limitations to Ad-based gene therapy. Since polycations have been shown to enhance adenovirus-mediated gene transfer in epithelial cells both in vitro and in vivo, we hypothesized that polycations could augment treatment efficacy in animals with established tumor. To address this hypothesis, protamine sulfate, a polycation already safely administered in humans, was complexed with a recombinant Ad (E1E3-deleted) vector containing the herpes simplex 1 thymidine kinase (HSVtk) suicide gene to treat cancer cell lines in vitro and in animals bearing intraperitoneal tumor. In the presence of 5 microg/ml protamine, the efficiency of gene transfer to a number of cancer cell lines normally resistant to adenovirus was significantly enhanced. **Protamine's** effect in vitro was found to be inversely proportional to the level of expression of the high affinity Ad binding site, coxsackievirus and adenovirus receptor (CAR), on the sur- face of the various cell lines tested. Ad.tk infected tumor cells were rendered 2.5- to three-fold more sensitive to 20 microM ganciclovir (GCV) in the presence of protamine. Protamine also augmented the in vivo transfer efficiency of the marker gene, LacZ (contained in an Ad vector), on the surface of tumors derived from an intraperitoneal mouse model. Quantitative imaging revealed 50% tumor surface transduced with LacZ when treatment was performed in the presence of 50 microg/ml protamine compared with 12% tumor surface in controls. However, experiments performed utilizing intraperitoneal administration of Ad.tk/GCV in the presence or absence of 50 microg/ml protamine demonstrated no significantly improved median survival in mice bearing established intraperitoneal tumors. Similarly, in Fischer rats bearing intrapleural tumor, no improvement in anti-tumor response was observed when Ad treatment was performed intrapleurally in the presence of protamine. Thus, although protamine induced an enhancement of Ad-mediated gene transfer in vitro and in vivo, its use as an adjunct to intracavitary Ad-based cancer gene therapy in vivo appears to be limited.

L6 ANSWER 5 OF 27 MEDLINE on STN

ACCESSION NUMBER: 1998173778 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9507068
TITLE: Protein kinase activities in ripening mango, Mangifera indica L., fruit tissue. I: Purification and characterization of a calcium-stimulated casein kinase-I.
AUTHOR: Frylinck L; Dubery I A
CORPORATE SOURCE: Department of Biochemistry, R.A.U.-University, Johannesburg, South Africa.
SOURCE: Biochimica et biophysica acta, **(1998 Jan 15)** 1382 (1) 65-79.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980408

AB A Ca(2+)-stimulated protein kinase (PK-I), active with dephosphorylated casein as exogenous substrate, was purified from ripening mango fruit. The purification procedure involved 30-70% ammonium sulphate fractionation and sequential anion exchange-, affinity-, hydrophobic interaction- and gel filtration chromatography. PK-I was purified ca. 40-fold with an overall yield of < 1%. The final specific activity in the presence of 0.1 mM Ca2+ was 55 nmol min-1 mg-1. Analysis of the most highly purified

preparations revealed a monomeric enzyme with an M(r) of 30.9 kDa and pI of 5.1. PK-I efficiently phosphorylated casein and phosvitin, but did not phosphorylate histone II-S, histone III-**S**, **protamine** sulphate or bovine serum albumin. PK-I activity was stimulated by micromolar concentrations of Ca2+ and was dependent on millimolar Mg2+ concentrations, which could not be substituted with Mn2+. PK-I activity was stimulated by, but was not dependent on Ca2+. Calmodulin and calmodulin inhibitors did not affect PK-I activity, but heparin and cAMP acted as inhibitors. The pH and temperature optima of the enzyme under standard reaction conditions were 6.5 and 35 degrees C, respectively. The kinetic reaction mechanism of PK-I was studied by using casein as substrate. Initial velocity and product inhibition studies with ADP as product inhibitor best fit an ordered bi-bi kinetic mechanism with the Mg(2+)-ATP complex binding first to the enzyme followed by binding of the protein substrate. The K(m)ATP and K(m)casein of PK-I were 9 microM and 0.26 mg ml-1, respectively. The KiADP of PK-I was 9 microM.

L6 ANSWER 6 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1998123841 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9462289
TITLE: Unusual chromatin structural organization in the sperm head of a murid rodent from southern Africa: the red veld rat, Aethomys chrysophilus type B.
AUTHOR: Breed W G
CORPORATE SOURCE: Department of Anatomical Sciences, University of Adelaide, Australia.
SOURCE: Journal of reproduction and fertility, **(1997 Nov)** 111 (2) 221-8.
Journal code: 0376367. ISSN: 0022-4251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980224

AB The structural organization of the chromatin of cauda epididymal spermatozoa of the red veld rat Aethomys chrysophilus type B was investigated by fluorescence microscopy after staining with DNA specific dyes and by transmission electron microscopy after incubation with Triton X100, dithiothreitol, and SDS. Staining with DNA dyes showed variation in intensity of fluorescence of the sperm chromatin, with an anterior spherical region staining far more intensely than the surrounding chromatin. Transmission electron microscopy of these spermatozoa indicated that this region was composed of cords and fibres. This chromatin region dispersed more readily than the surrounding chromatin when spermatozoa were incubated with the detergents, and it is suggested that, unlike the rest of the sperm chromatin, it may be a histone-rich region, with **protamine**(**s**) being either scarce or absent.

L6 ANSWER 7 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1998097880 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9435591
TITLE: Heparin/heparan sulfate chelation inhibits control of vascular repair by tissue-engineered endothelial cells.
AUTHOR: Han R O; Ettenson D S; Koo E W; Edelman E R
CORPORATE SOURCE: Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, Cambridge 02139, USA.
CONTRACT NUMBER: GM/HL-49039 (NIGMS)
SOURCE: American journal of physiology, **(1997 Dec)** 273 (6 Pt 2) H2586-95.

Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980209

AB The relative importance of heparin-like compounds in mediating vascular repair is unclear. We investigated how protamine, a chelator of heparin, affected endothelial cell inhibition of vascular smooth muscle cell growth and intimal hyperplasia. The 52% ($P < 0.001$) reduction in smooth muscle cell proliferation produced by postconfluent endothelial cell-conditioned medium was entirely reversed by pretreatment of medium with heparinase and heparitinase and was inhibited in a dose-dependent fashion by the coadministration of protamine. Pretreatment of conditioned medium with heparinase and heparitinase largely prevented **protamine's** mitogenic activity, suggesting that protamine affects growth by interacting with heparin-like compounds. Perivascular implantation of polymerengrafted endothelial cells reduced neointima formation in denuded rat carotid arteries by 92% ($P < 0.001$) and cell proliferation by 81% ($P < 0.001$). Coadministration of protamine abolished the inhibitory potential of the cell implants, resulting in a nearly twofold exacerbation of intimal hyperplasia compared with controls ($P < 0.001$). Thus heparin-like molecules are essential to the biochemical regulation of vascular repair provided by endothelial cells, and the continued routine clinical use of heparin chelators, like protamine, may be questionable.

L6 ANSWER 8 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1998010146 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9349433
TITLE: Protamine sulfate enhances lipid-mediated gene transfer.
AUTHOR: Sorgi F L; Bhattacharya S; Huang L
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh School of Medicine, PA 15261, USA.
CONTRACT NUMBER: CA 59327 (NCI)
CA 64654 (NCI)
CA 71731 (NCI)
+
SOURCE: Gene therapy, **(1997 Sep)** 4 (9) 961-8.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971120

AB A polycationic peptide, protamine sulfate, USP, has been shown to be able to condense plasmid DNA efficiently for delivery into several different types of cells in vitro by several different types of cationic liposomes. The monovalent cationic liposomal formulations (DC-Chol and lipofectin) exhibited increased transfection activities comparable to that seen with the multivalent cationic liposome formulation, lipofectamine. This suggests that lipofectamine's superior in vitro activity arises from its ability to condense DNA efficiently and that **protamine's** primary role is that of a condensation agent, although it also possesses several amino acid sequences resembling that of a nuclear localization signal. While the use of polycations to condense DNA has been previously reported, the of protamine sulfate, USP as a condensation agent was found to be superior to poly-L-lysine as well as to various other types of

protamine. These differences among various salt forms of protamine appear to be attributable to structural differences between the protamines and not due to differences in the net charge of the molecule. The appearance of lysine residues within the protamine molecule correlate with a reduction in binding affinity to plasmid DNA as well as an observed loss in transfection enhancing activity. This finding sheds light on the structural requirements of condensation agents for use in gene transfer protocols. Furthermore, protamine sulfate, USP is an FDA-approved compound with a documented safety profile and could be readily used as an adjuvant to a human gene therapy protocol.

L6 ANSWER 9 OF 27 MEDLINE on STN
ACCESSION NUMBER: 95397349 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7667826
TITLE: Studies on the neutralizing effects of protamine on unfractionated and low molecular weight heparin (Fragmin) at the site of activation of the coagulation system in man.
AUTHOR: Wolzt M; Weltermann A; Nieszpaur-Los M; Schneider B; Fassolt A; Lechner K; Eichler H G; Kyrle P A
CORPORATE SOURCE: Department of Clinical Pharmacology, Institute for Medical Statistics and Documentation, Vienna, Austria.
SOURCE: Thrombosis and haemostasis, **(1995 Mar)** 73 (3) 439-43.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 19951020
Entered Medline: 19951011

AB In a double-blind, randomized, cross-over study the neutralizing action of protamine towards unfractionated heparin (UFH, 150 U/kg i.v.) and a low molecular weight heparin (LMWH, Fragmin, 100 anti-Xa U/kg i.v.) was investigated in 15 healthy subjects in vitro by measuring activated partial thromboplastin time (APTT), thrombin time (TT) and anti factor Xa activity (anti-Xa) in venous blood and in vivo by determination of prothrombin fragment 1.2 (f1.2) and thrombin-antithrombin III complexes (TAT) in venous blood and in shed blood. UFH and LMWH caused a prolongation of APTT and TT, an increase in anti-Xa and significantly inhibited f1.2 and TAT formation in shed blood, whereas only a minimal effect on TAT and f1.2 formation in venous blood was noted. Administration of 1 mg protamine/100 U UFH resulted in a near complete reversal of APTT, TT and anti-Xa, whereas lower doses (0.25 and 0.5 mg) were less effective. The effects of UFH on f1.2 and TAT generation in shed blood were partially (60-70%) neutralized only by the high dose (1.0 mg). Application of 1 mg protamine/100 anti-Xa U LMWH caused a near complete reversal of both APTT and TT but had only a weak effect on anti-Xa. In shed blood, the effect of LMWH on TAT and f1.2 formation was reversed by protamine only by 14% and 23% respectively. Our data do not support the concept that to reduce the incidence of **protamine's** potential clinical side effects, the administration of a lower dose of protamine than 1 mg protamine/100 U UFH is justified.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 10 OF 27 MEDLINE on STN
ACCESSION NUMBER: 95138146 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7836415
TITLE: Expression and characterization of PKD, a phorbol ester and diacylglycerol-stimulated serine protein kinase.

AUTHOR: Van Lint J V; Sinnett-Smith J; Rozengurt E
CORPORATE SOURCE: Growth Regulation Laboratory, Imperial Cancer Research Fund, London, United Kingdom.
SOURCE: Journal of biological chemistry, **(1995 Jan 20)** 270 (3) 1455-61.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19950314
Entered Medline: 19950224

AB A novel protein kinase (named PKD) with an NH2-terminal region containing two cysteine-rich motifs has been expressed in COS-7 cells and identified as a receptor for phorbol esters. COS-7 cells transfected with a PKD cDNA construct (pcDNA3-PKD) exhibit a marked (4.8-fold) increase in [3H]phorbol 12,13-dibutyrate binding. An antiserum raised against the COOH-terminal 15 amino acids of PKD specifically recognized a single 110-kDa band in PKD-transfected cells. PKD prepared by elution from immunoprecipitates with the immunizing peptide efficiently phosphorylated the synthetic peptide syntide-2. The enzyme only poorly phosphorylated a variant syntide-2 where arginine 4 has been replaced by an alanine. The addition of [3H]phorbol 12,13-dibutyrate, 1-oleoyl-2-acetylglycerol, or 1,2-dioctanoyl-sn-glycerol in the presence of dioleoylphosphatidylserine stimulated the syntide-2 kinase activity of PKD in a synergistic fashion (4-6-fold). Furthermore, the autophosphorylation of PKD was strikingly stimulated by the same lipid activators (14-24-fold). Similar properties were found with PKD isolated from mouse lung. The substrate specificity of PKD is different from that of previously identified members of the protein kinase C family since it does not efficiently phosphorylate histone III-**S**, **protamine** sulfate, or a synthetic peptide based upon the conserved pseudosubstrate region of the protein kinase C family. Taken together, these data unambiguously establish PKD as a phorbol ester receptor and as a novel phospholipid/diacylglycerol-stimulated protein kinase.

L6 ANSWER 11 OF 27 MEDLINE on STN
ACCESSION NUMBER: 94093178 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8268631
TITLE: Tissue distribution, circulating half-life, and excretion of intravenously administered protamine sulfate.
AUTHOR: DeLucia A 3rd; Wakefield T W; Kadell A M; Wrobleski S K; VanDort M; Stanley J C
CORPORATE SOURCE: Jobst Vascular Laboratory, Department of Surgery, University of Michigan Medical Center, Ann Arbor 48109-0329.
SOURCE: ASAIO journal (American Society for Artificial Internal Organs : 1992), **(1993 Jul-Sep)** 39 (3) M715-8.
Journal code: 9204109. ISSN: 1058-2916.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940215
Last Updated on STN: 19940215
Entered Medline: 19940131

AB Intravenous protamine reversal of heparin anticoagulation may cause adverse hemodynamic side effects, but little is known about **protamine's** tissue distribution, circulating half-life (t/2), and excretion. The latter were assessed by examining 125I

Bolton-Hunter (125I BH) radiolabeled protamine kinetics in a rat model. Three groups were studied: Group I controls (n = 5) received intravenous 125I BH label alone; Group II (n = 10) received intravenous 125I BH radiolabeled protamine (0.15 mg/100 g); and Group III (n = 10) received intravenous heparin (15 IU/100 g) followed by intravenous 125I BH radiolabeled protamine (0.15 mg/100 g). Five animals in each group were killed at 3 min, and tissue radioactivity was quantitated. An additional five animals each in Groups II and III were followed up for 60 min to determine **protamine's** circulating t/2 and its renal excretion. The lungs, heart, and kidneys, compared with other organs, retained the most 125I BH radiolabeled protamine per gram tissue at 3 min. Retention of 125I BH radiolabeled protamine (Groups II & III) was greater ($p < 0.05$, Kruskal-Wallis) than control 125I BH label alone (Group I). Higher tissue 125I activity was observed in Group II than in Group III rats, suggesting that tissue retention of protamine was greater in the absence of prior heparin administration. Circulating t/2 was shorter (18 vs. 24 min) and urinary protamine 125I excretion was higher (34 vs. 24%) in Group III than in Group II, respectively, suggesting more rapid renal clearance of protamine in the presence of heparin.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 12 OF 27 MEDLINE on STN
ACCESSION NUMBER: 92318351 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1619724
TITLE: Heparin-mediated reductions of the toxic effects of protamine sulfate on rabbit myocardium.
AUTHOR: Wakefield T W; Wrobleski S K; Nichol B J; Kadell A M; Stanley J C
CORPORATE SOURCE: Jobst Vascular Research Laboratories, Department of Surgery, University of Michigan Medical Center, Ann Arbor 48109-0329.
SOURCE: Journal of vascular surgery : official publication, Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, **(1992 Jul)** 16 (1) 47-53.
Journal code: 8407742. ISSN: 0741-5214.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920815
Last Updated on STN: 19920815
Entered Medline: 19920805

AB Protamine sulfate causes direct myocardial suppression when used to reverse heparin anticoagulation. **Protamine's** excessive positive charge accompanying its surface arginine groups appears to be responsible for this toxicity. This study was designed to assess the hypothesis that negatively charged heparin given after protamine exposure may enhance the recovery of protamine-induced myocardial dysfunction. Isolated rabbit hearts (n = 20) were perfused with physiologic saline solution at 80 to 90 mm Hg containing high dose protamine, 250 micrograms/ml, until heart contraction essentially ceased (baseline). Hearts were then randomly reperfused for 15 minutes with either physiologic saline solution (group I, n = 10) or heparin plus physiologic saline solution (group II, n = 10) at a dose of 0.1 IU/1.0 microgram of previously administered protamine. Developed left ventricular blood pressure, heart rate, pulmonary artery PaO2, contractility (+dp/dt), oxygen extraction (AvO2), oxygen consumption (VO2), and rate x pressure product were assessed. A protective, beneficial response accompanied heparin administration (group II) in all functions assessed except blood pressure. Maximum changes, comparing group I with II, were heart rate (beats/min) -72 versus -1, p less than

0.001; +dp/dt -64% versus -51%, p less than 0.01; PaO2 +86% versus +9%, p less than 0.001; AvO2 -37% versus -4%, p less than 0.001; VO2 -50% versus -28%, p less than 0.008; and rate x pressure product -73% versus -51%, p less than 0.001. These data suggest a separation of **protamine's** hemodynamic effects (blood pressure) and metabolic effects (VO2). Furthermore, these data support the tenet that heparin is able to markedly lessen the toxic myocardial effects of protamine.

L6 ANSWER 13 OF 27 MEDLINE on STN
ACCESSION NUMBER: 91245789 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2038184
TITLE: Increased prostacyclin and adverse hemodynamic responses to protamine sulfate in an experimental canine model.
AUTHOR: Wakefield T W; Wrobleski S K; Wirthlin D J; Wang T W; Stanley J C
CORPORATE SOURCE: Jobst Vascular Research Laboratories, Department of Surgery, University of Michigan, Ann Arbor 48109.
SOURCE: Journal of surgical research, **(1991 May)** 50 (5) 449-56.
Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 19910719
Last Updated on STN: 19980206
Entered Medline: 19910628

AB Prostanoid activity was correlated with the hemodynamic effects of protamine sulfate reversal of heparin in 24 dogs undergoing three different pretreatment regimens: Group I (n = 8) received saline, Group II (n = 8) received the thromboxane synthetase inhibitor U63,557A (30 mg/kg), and Group III (n = 8) received indomethacin (10 mg/kg). Pretreatment substances were administered as 5-min intravenous infusions 20 min before anticoagulation with intravenous heparin (150 IU/kg). Protamine sulfate (1.5 mg/kg) was subsequently given as a 10-sec intravenous infusion 30 min after heparin had been administered. Hemodynamic data, as well as prostacyclin (PGI2) and thromboxane (TxA2) activity in aortic, venous, and pulmonary artery blood samples, were assessed over a 30-min time period following protamine administration. Group III indomethacin pretreatment provided the most protection from declines in blood pressure, heart rate, cardiac output, venous oxygen saturation, oxygen consumption, and elevations in pulmonary pressures and was accompanied with actual declines in PGI2. Group II U63,557A pretreatment was associated with the most severe hemodynamic changes and the greatest increase in PGI2 (+576%). Elevated PGI2 correlated with hypotension at 1 and 3 min (P less than 0.01), as well as pulmonary artery pressure declines at all times following protamine reversal. TxA2 changes did not correlate with hemodynamic changes. **Protamine's** adverse hemodynamic responses were attenuated with cyclooxygenase blockade by indomethacin, but were worsened with selective TxA2 blockade with U63,557A. Excess arachadonic acid precursors in the latter setting may increase PGI2 production. This study, for the first time, raises the possibility that PGI2 contributes to the adverse effects accompanying protamine reversal of heparin anticoagulation.

L6 ANSWER 14 OF 27 MEDLINE on STN
ACCESSION NUMBER: 89088335 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3207794
TITLE: Interspecies differences in the stability of mammalian sperm nuclei assessed in vivo by sperm microinjection and in vitro by flow cytometry.
AUTHOR: Perreault S D; Barbee R R; Elstein K H; Zucker R M; Keefer

C L
CORPORATE SOURCE: Reproductive Toxicology Branch, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.
SOURCE: Biology of reproduction, **(1988 Aug)** 39 (1) 157-67.
Journal code: 0207224. ISSN: 0006-3363.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198902
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19890223

AB To assess the structural stability of mammalian sperm nuclei and make interspecies comparisons, we microinjected sperm nuclei from six different species into hamster oocytes and monitored the occurrence of sperm nuclear decondensation and male pronucleus formation. The time course of sperm decondensation varied considerably by species: human and mouse sperm nuclei decondensed within 15 to 30 min of injection, and chinchilla and hamster sperm nuclei did so within 45 to 60 min, but bull and rat sperm nuclei remained intact over this same period of time. Male pronuclei formed in oocytes injected with human, mouse, chinchilla, and hamster sperm nuclei, but rarely in oocytes injected with bull or rat sperm nuclei. However, when bull sperm nuclei were pretreated with dithiothreitol (DTT) in vitro to reduce protamine disulfide bonds prior to microinjection, they subsequently decondensed and formed pronuclei in the hamster ooplasm. Condensed rat spermatid nuclei, which lack disulfide bonds, behaved similarly. The same six species of sperm nuclei were induced to undergo decondensation in vitro by treatment with DTT and detergent, and the resulting changes in nuclear size were monitored by phase-contrast microscopy and flow cytometry. As occurred in the oocyte, human sperm nuclei decondensed the fastest in vitro, followed shortly by chinchilla, mouse, and hamster and, after a lag, by rat and bull sperm nuclei. Thus species differences in sperm nuclear stability exist and appear to be related to the extent and/or efficiency of disulfide bonding in the sperm nuclei, a feature that may, in turn, be determined by the type(s) of sperm nuclear **protamine(s)** present.

L6 ANSWER 15 OF 27 MEDLINE on STN
ACCESSION NUMBER: 88264270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3387950
TITLE: The effect of protamine sulfate on platelet function.
AUTHOR: Lindblad B; Wakefield T W; Whitehouse W M Jr; Stanley J C
CORPORATE SOURCE: Department of Surgery, University of Michigan Medical School, Ann Arbor.
SOURCE: Scandinavian journal of thoracic and cardiovascular surgery, **(1988)** 22 (1) 55-9.
Journal code: 0121343. ISSN: 0036-5580.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880729

AB The adverse effects of protamine sulfate, used to neutralize the anticoagulant action of heparin, include systemic hypotension, pulmonary artery hypertension, thrombocytopenia and leukopenia. For further evaluation of **protamine's** mechanism of action, a three-part investigation was performed. In part I platelet-rich plasma

(PRP) was prepared from canine blood samples (n = 6) taken before and 2 minutes after injection of protamine. In part II human PRP (n = 5) was preincubated with protamine or distilled water. Adenosine diphosphate-induced aggregation of protamine-treated platelets was unchanged, but thrombin-induced aggregation was inhibited in both canine and human preparations (p less than 0.05). In part III thrombocytopenia was produced in splenectomized dogs (n = 5), using microporous filters, to 4.5-8.4% of the initial platelet count. Protamine reversal of the heparinization caused hypotension (maximally -29 mmHg 90 s after protamine), but not pulmonary arterial hypertension. Leukopenia developed before additional thrombocytopenia appeared. Protamine-platelet interaction inhibits thrombin-induced platelet aggregation. Platelets may play an important role in the pulmonary pressure rise during protamine reversal, but do not mediate the systemic hypotension.

L6 ANSWER 16 OF 27 MEDLINE on STN
ACCESSION NUMBER: 86128986 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4091464
TITLE: The effect of inhibition of angiogenesis in granulation tissue on wound healing and the fibroblast.
AUTHOR: McGrath M H; Emery J M 3rd
SOURCE: Annals of plastic surgery, **(1985 Aug)** 15 (2) 105-22.
Journal code: 7805336. ISSN: 0148-7043.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860224

AB Protamine sulfate given in high doses can inhibit angiogenesis in the granulation tissue generated in an open wound. This is reflected by changes consistent with delayed vascular maturation in the morphology of the regenerating vessels seen at the gross, microscopic, and ultrastructural levels. A coincidental delay in wound healing as evidenced by impaired wound contraction occurs, although fibroblast duplication and myofibroblast differentiation appear intact. However, the fibroblasts contain little endoplasmic reticulum, the site of synthetic activity, and the surrounding collagen appears loose and disorganized. To unite these observations into a coherent pattern, we review the proposal that the endothelial cell, the fibroblast, and the extracellular stroma are interdependent and that maturation of each is necessary to maintain the momentum of wound healing. Our findings fit this mechanistic hypothesis but do not prove it. The abnormal vasoformation that may be initiated by **protamine's** anticoagulant properties could set the stage for impaired fibroblast synthetic activity. If collagenous stroma is deficient, both endothelial maturation and wound contraction wound fail. Although we saw these final events, to prove a series of cause and effect changes would require further study of the oxygen tension and the fibrin and collagen levels in granulation tissue.

L6 ANSWER 17 OF 27 MEDLINE on STN
ACCESSION NUMBER: 55035544 MEDLINE
DOCUMENT NUMBER: PubMed ID: 13223836
TITLE: [Heparinoid substances. I. Value of Allen's **protamine** sulfate titration as routine method in x-ray exposure].
Heparinoide stoffen. I. De waarde van de protaminesulfaattitratie volgens Allen als routinemethode bij bestraalde personen.
AUTHOR: DE VRIES S I; VAN DAELEN C C

SOURCE: Nederlands tijdschrift voor geneeskunde, **(1954 Oct 23)** 98 (43) 3051-6.
Journal code: 0400770. ISSN: 0028-2162.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Dutch
FILE SEGMENT: OLDMEDLINE
OTHER SOURCE: CLML5527-35770-378-408-442
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20040200
Last Updated on STN: 20040200
Entered Medline: 20030501

L6 ANSWER 18 OF 27 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:143558 BIOSIS
DOCUMENT NUMBER: PREV199191080098; BA91:80098
TITLE: PROTAMINE HEPARIN-INDUCED PULMONARY HYPERTENSION IN PIGS EFFECTS OF TREATMENT WITH A THROMBOXANE RECEPTOR ANTAGONIST ON HEMODYNAMICS AND COAGULATION.
AUTHOR(S): NUTTALL G A [Reprint author]; MURRAY M J; BOWIE E J W
CORPORATE SOURCE: DEP ANESTHESIOLOGY, MAYO CLINIC, ROCHESTER, MINN 55905, USA
SOURCE: Anesthesiology (Hagerstown), (1991) Vol. 74, No. 1, pp. 138-145.
CODEN: ANESAV. ISSN: 0003-3022.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 14 Mar 1991
Last Updated on STN: 15 Mar 1991

AB Adverse hemodynamic reactions after protamine neutralization of heparin are an infrequent but important clinical problems. Pretreatment of swine with a thromboxane A2 receptor antagonist has been reported to prevent the pulmonary hypertensive response occasionally seen after protamine reversal of heparin anticoagulation. In the current study, a control group of pigs (n = 9), received intravenous heparin (300 IU/kg), followed after 10 min by a neutralizing dose of protamine (3 mg/kg). A treatment group of pigs (n = 11) was treated identically, except that the thromboxane A2 receptor antagonist L-670596 (2 mg/kg) was infused intravenously 2 min after the protamine infusion. Hemodynamic and coagulation profiles were monitored during these procedures. Pulmonary hypertension developed and reached a peak within 2 min of protamine administration, often at the same time that L-670596 was administered in the treatment group. There was no statistical difference between control and treament groups' peak pulmonary arterial pressure and peak pulmonary vascular resistance. However, the interval for return of mean pulmonary artery pressure from peak to baseline values was 11.6 ± 3.1 versus 5.5 ± 1.9 min (mean ± SD) for control and treatment groups, respectively ($P < 0.01$). Thromboxane B2 plasma concentrations increased in both groups and were correlated with the pulmonary hypertensive resposne ($r = 0.86$, $P < 0.01$). Platelet aggregation to collagen was inhibited by the thromboxane A2 receptor antagonist ($P < 0.05$). Bleeding time was prolonged beyond normal range in 50% of L-670596-treated pigs. All other coagulation tests in both groups returned to baseline after reversal of heparin with protamine and were unaffected by L-670596. Selective TxA2 receptor antagonists may have a role in managing **protamine's** adverse hemodynamic disturbances.

L6 ANSWER 19 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002091358 EMBASE
TITLE: Protamine inhibits tissue factor-initiated extrinsic coagulation.
AUTHOR: Chu A.J.; Wang Z.-G.; Raicu M.; Beydoun S.; Ramos N.
CORPORATE SOURCE: Dr. A.J. Chu, 416 Lande Medical Research Building, 550 E.

Canfield, Detroit, MI 48201, United States.
ad5742@wayne.edu
SOURCE: British Journal of Haematology, (2001) 115/2 (392-399).
Refs: 33
ISSN: 0007-1048 CODEN: BJHEAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The enhanced extrinsic coagulation in response to inflammation could contribute to disseminated intravascular coagulation, often manifesting cardiovascular complications. The complex mechanism remains unclear and effective management is not well established. The ability of protamine to offset bacterial endotoxin (LPS)-induced tissue factor (TF)-initiated extrinsic coagulation was demonstrated in human peripheral blood monocytes and cultured human leukaemia THP-1 monocytes, which was consistent with the inhibition of rabbit brain thromboplastin (rbTF) procoagulant activity in a cell-free in vitro model. Protamine significantly prolonged prothrombin time, further confirming the downregulation of the extrinsic pathway. However, thrombin time remained unaltered. Chromogenic assays were performed to dissect the extrinsic pathway, identifying inhibitory site(**s**). **Protamine** significantly inhibited factor VII (FVII) activation but not the dissected FX activation. The amidolytic activities of FVIIa and FXa were unaffected. The inhibited FVII activation in the presence of protamine was confirmed by the diminished FVIIa formation on Western blot analyses. Protamine preferentially inhibited TF-catalysed FVII activation, downregulating the extrinsic cascade. Protamine could be of anticoagulant significance in the management of the extrinsic hypercoagulation.

L6 ANSWER 20 OF 27 EMBASE
on STN
ACCESSION NUMBER: 1998251125 EMBASE
TITLE: Structural characterization and functional effects of a circulating heparan sulfate in a patient with hepatocellular carcinoma.
AUTHOR: Wages D.S.; Staprans I.; Hambleton J.; Bass N.M.; Corash L.
CORPORATE SOURCE: D.S. Wages, Cerus Corporation, 2525 Stanwell Drive, Concord, CA 94520, United States
SOURCE: American Journal of Hematology, (1998) 58/4 (285-292).
Refs: 29
ISSN: 0361-8609 CODEN: AJHEDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A circulating anticoagulant was isolated from the plasma of a 42-year- old man with cirrhosis and hepatocellular carcinoma who had an unusual coagulation test profile. The patient developed a fatal coagulopathy, unresponsive to protamine therapy or plasma exchange following liver biopsy. However, at presentation, routine hemostasis assays were normal. The patient had mucocutaneous bleeding but the sole laboratory abnormality was a prolonged thrombin time (TT = 99 s, normal 25-35 **s**). **Protamine** titration indicated activity equivalent to a heparin concentration of 6-7 U/ml. Antithrombin III (AT III) antigen and activity were markedly elevated. The anticoagulant activity, purified from plasma by DEAE chromatography, was identified as a glycosaminoglycan (GAG). GAG

anti-thrombin activity was completely abolished by heparin lyase III. Based on the degree of sulfation and HPLC pattern, the GAG was classified as heparan sulfate. Low levels (4 μM) of purified GAG markedly prolonged the TT (>120 s) but not the activated partial thromboplastin time (PTT) (31.4 s). In a Factor Xa assay, the GAG exhibited a potency equivalent to 0.06 U of low molecular weight heparin per nmol of uronic acid. Patients with endogenous circulating glycosaminoglycans can present with unusual laboratory coagulation test profiles. These reflect complex dysfunction of hemostasis, leading to difficulty in providing diagnosis and effective care.

L6 ANSWER 21 OF 27 EMBASE
on STN

ACCESSION NUMBER: 83113644 EMBASE
DOCUMENT NUMBER: 1983113644
TITLE: Electrical charge. Its role in the pathogenesis and prevention of experimental membranous nephropathy in the rabbit.
AUTHOR: Adler S.G.; Wang H.; Ward H.J.; et al.
CORPORATE SOURCE: Dep. Med., Harbor-UCLA Med. Cent., Torrance, CA 90509, United States
SOURCE: Journal of Clinical Investigation, (1983) 71/3 (487-499). CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 028 Urology and Nephrology
026 Immunology, Serology and Transplantation
LANGUAGE: English

AB Intravenous cationic bovine serum albumin (BSA, pI > 9.5) induces membranous nephropathy in immunized rabbits. In this study, unimmunized rabbits received intravenous injections of cationic (n = 3) or native (n = 3) BSA, followed by ex vivo isolated left renal perfusions with sheep anti-BSA antibody. Capillary wall deposits of IgG and C3 were seen exclusively in the group receiving cationic BSA, confirming an in situ pathogenesis for cationic, BSA-induced membranous nephropathy, and demonstrating the importance of a cationic antigen for its production. We then explored whether membranous nephropathy in this model is prevented by the concomitant injection of protamine sulfate, a filterable, relatively non-immunogenic polycation. An in vitro study demonstrated that protamine sulfate incubated with glomerular basement membrane (GBM) decreased the subsequent binding of radiolabeled cationic BSA ($P < 0.05$). In vivo, protamine sulfate was shown to bind to anionic sites in the glomerular capillary wall after intravenous injection. Groups of rabbits received 3 wk of daily intravenous injections of cationic BSA alone (n = 15) or cationic BSA and protamine (n = 18). After 2 wk of injection of cationic BSA alone, typical membranous nephropathy developed. Granular deposits of IgG and C3 were present along the GBM associated with subepithelial dense deposits, foot process effacement, and marked albuminuria. Protamine significantly reduced or prevented the formation of deposits ($P < 0.001$) and in 6 of 18 protamine-treated animals, existing deposits decreased or disappeared between 2 and 3 wk of injection. Albuminuria was significantly reduced in protamine-treated animals with a mean of 124 ± 55 mg/24 h compared to 632 ± 150 mg/24 h in the control group receiving cationic BSA alone. No significant differences between the groups were noted in serum levels of IgG, C3, anti-BSA antibody, or circulating immune complex size. Studies in additional animals (n = 5) given radiolabeled cationic BSA showed that protamine did not alter the clearance of cationic BSA from serum. Control experiments showed that **protamine's** beneficial effects were not related to its weak anticoagulant property or to its theoretical ability to deplete tissue histamine. The administration of heparin (n = 6) or diphenhydramine (n = 6) had no effect on the development of the epimembranous lesion compared to the group receiving BSA alone. In addition, homogenized kidney histamine content was not

significantly different in the group receiving cationic BSA alone compared to the group receiving cationic BSA and protamine. This work shows that a cationic BSA-induced glomerular lesion can be produced by a renal perfusion technique involving in situ complex formation and that this process requires a cationic antigen for its development. We believe that the demonstrated beneficial effects of protamine are due to its ability to bind to glomerular anionic sites, and that this electrostatic interaction results in inhibition for the further binding of the cationic antigen, thereby limiting the severity of glomerulonephritis in this model.

L6 ANSWER 22 OF 27 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 138:126876 CA
TITLE: Enhancement of gene delivery by listeriolysin O/protamine/plasmid DNA complex
AUTHOR(S): Saito, G.; Amidon, G. L.; Lee, K. D.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Proceedings - 28th International Symposium on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference, San Diego, CA, United States, June 23-27, 2001 (**2001**), Volume 2, 1233-1234. Controlled Release Society: Minneapolis, Minn.
CODEN: 69CNY8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Listeriolysin O (LLO), an endosomolytic protein from Listeria monocytogenes, was exploited in plasmid DNA delivery. The single Cys of LLO was conjugated to protamine via a disulfide bond. LLO-s-**s-protamine** was hemolytically active only when LLO was released from protamine upon reduction of the cysteine. Complexes containing plasmid DNA, protamine, and LLO-s-**s-protamine** were tested for their enhanced gene delivery efficiency in in vitro transfection expts. using luciferase and GFP reporter genes. Replacing ≤ 1% of protamine with LLO-s-**s-protamine** resulted in close to 3 orders of magnitude improvement in luciferase gene expression over protamine/DNA complexes.

L6 ANSWER 23 OF 27 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 117:225821 CA
TITLE: Adhesion of Pseudomonas aeruginosa to human bladder epithelial cells and the influence of protamine on this attachment
AUTHOR(S): Boussard, P.; Devleeschouwer, M. J.; Dony, J.
CORPORATE SOURCE: Inst. Pharm., Univ. Libre Bruxelles, Brusselles, B-1050, Belg.
SOURCE: Pharmaceutica Acta Helvetiae (**1992**), 67(9-10), 259-64
CODEN: PAHEAA; ISSN: 0031-6865
DOCUMENT TYPE: Journal
LANGUAGE: French
AB The authors studied the effect of protamine on the adhesion of Pseudomonas aeruginosa to human bladder epithelial cells. The presence of subinhibitory concns. of protamine reduced bacterial adhesion to 20% of that observed in its absence. Protamine appears to act by binding to adhesins in a rapid and stable fashion. **Protamine's** low toxicity and its ability to prevent bacterial colonization may indicate its utility as an antibacterial agent.

L6 ANSWER 24 OF 27 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 97:106167 CA
TITLE: Mechanism of regulation of enzymic phosphorylation of proteins. 3. Probable mechanism of the interaction

of the protein modulator with components of the phosphotransferase reaction

AUTHOR(S): Baba-Zade, S. N.; Sadykhov, S. T.; Akhmedli, K. M.; Mekhtiev, N. Kh.

CORPORATE SOURCE: Nauchn. Tsentr. Biol. Issled., Baku, USSR

SOURCE: Izvestiya Akademii Nauk Azerbaidzhanskoi SSR, Seriya Biologicheskikh Nauk (**1981**), (5), 99-107
CODEN: IABLAQ; ISSN: 0132-6112

DOCUMENT TYPE: Journal

LANGUAGE: Russian

AB Kinetic data on protamine phosphorylation in the presence of ATP and in the presence or absence of protein kinase modulator protein from prawn tissue were compared with predicted values given by computer evaluation of 6 math. models representing possible reaction mechanisms. In the absence of modulator, the mechanism giving the best fit of calculated and exptl. values assumed that **protamine** (**S**) and ATP (A) could bind to the enzyme (E) in any order to give a complex EAS, in equilibrium with binary complexes (ES.dblarw.EAS, EA.dblarw.EAS), which breaks down to give products. The simplest scheme accounting for the effect of modulator protein involved the same assumptions about formation of the EAS complex, but assumed further that the productive complex differed from EAS (EAS*), and that the rate of breakdown of EAS* depended on modulator concentration

L6 ANSWER 25 OF 27 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 52:21451 CA

ORIGINAL REFERENCE NO.: 52:3901f-h

TITLE: The effect of chemicals on the agglutination reaction

AUTHOR(S): Lisowski, Jozef

CORPORATE SOURCE: Inst. Immunol. Terap. Doswiadczalnej PAN, Wroclaw, Pol.

SOURCE: Arch. Immunol. Terap. Doswiadczalnej (**1956**), 4, 57-65

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB Red-cell agglutination of human A and B groups by anti-A and -B serums was inhibited by M ethanolamine and 0.6M triethanolamine in 5 hrs. of incubation, and saturated lecithin solution in 3 hrs. of incubation, but was unaffected by tris(hydroxymethyl)aminomethane (0.00013-0.13M), serine (0.0002-0.2M), cephalins (saturated), choline (0.00015-0.15M), Na oleate (0.000033-0.0033M), Na palmitate (0.00002-0.002M), Na stearate (0.000016-0.0016M), **protamine S** (0.000118-1.18% by weight), heparin (8.3-830 L.U./ml.), saponin (0.0001-0.001%), strychnine (0.000015-0.015M), thiamine chloride (0.0007-0.07M), adenosine (0.0007-0.07M), Na adenosinetriphosphate (0.00055-0.055M), nicotinamide (0.0005-0.5M), veronal (0.0005-0.5M), creatine (0.0009-0.09M), tannin (0.00012-0.12M), thioglycolic acid (0.00011-0.11M), thiourea (0.00017-0.17M), and Nitrogranulogen (0.0007-0.07M).

L6 ANSWER 26 OF 27 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 1998:174860 SCISEARCH

THE GENUINE ARTICLE: YY550

TITLE: Protein kinase activities in ripening mango, Mangifera indica L., fruit tissue - I: Purification and characterization of a calcium-stimulated casein kinase-I

AUTHOR: Frylinck L; Dubery I A (Reprint)

CORPORATE SOURCE: RAU UNIV, DEPT BIOCHEM, POB 524, ZA-2006 JOHANNESBURG, SOUTH AFRICA (Reprint); RAU UNIV, DEPT BIOCHEM, ZA-2006 JOHANNESBURG, SOUTH AFRICA

COUNTRY OF AUTHOR: SOUTH AFRICA

SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEIN STRUCTURE AND MOLECULAR ENZYMOLOGY, (**15 JAN 1998**) Vol. 1382, No. 1, pp. 65-79.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE

AMSTERDAM, NETHERLANDS.
ISSN: 0167-4838.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A Ca2+-stimulated protein kinase (PK-I), active with dephosphorylated casein as exogenous substrate, was purified from ripening mango fruit. The purification procedure involved 30-70% ammonium sulphate fractionation and sequential anion exchange-, affinity-, hydrophobic interaction-and gel filtration chromatography. PK-I was purified ca. 40-fold with an overall yield of < 1%. The final specific activity in the presence of 0.1 mM Ca2+ was 55 nmol min(-1) mg(-1). Analysis of the most highly purified preparations revealed a monomeric enzyme with an M-r of 30.9 kDa and pI of 5.1. PK-I efficiently phosphorylated casein and phosvitin, but did not phosphorylate histone II-S, histone III-**S**, **protamine** sulphate or bovine serum albumin. PK-I activity was stimulated by micromolar concentrations of Ca2+ and was dependent on millimolar Mg2+ concentrations, which could not be substituted with Mn2+. PK-I activity was stimulated by, but was not dependent on Ca2+. Calmodulin and calmodulin inhibitors did not affect PK-I activity, but heparin and cAMP acted as inhibitors, The pH and temperature optima of the enzyme under standard reaction conditions were 6.5 and 35 degrees C, respectively. The kinetic reaction mechanism of PK-I was studied by using casein as substrate. Initial velocity and product inhibition studies with ADP as product inhibitor best fit an ordered bi-bi kinetic mechanism with the Mg2+-ATP complex binding first to the enzyme followed by binding of the protein substrate. The K(m)ATP and K(m)casein of PK-I were 9 mu M and 0.26 mg ml(-1), respectively. The K(i)ADP of PK-I was 9 mu M. (C) 1998 Elsevier Science B.V.